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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/444,144	11/20/99	HOWELL M	CYT0001

EXAMINER	
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1642	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/444,144	Howel et al
Examiner	**Group Art Unit**
Larry R. Helms Ph.D.	1642

☒ Responsive to communication(s) filed on *13 Jun 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-49* is/are pending in the applicat

Of the above, claim(s) *4, 6-9, 28-33, and 44-49* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-3, 5, 10-27, and 34-43* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1-43 and the election of species of an inert medium of a macroporous bead, inhibitor of soluble receptors for tumor necrosis factor alpha, and binding partner is an antibody, in Paper No. 6 is acknowledged. Upon further reconsideration no election of species is needed for the biological fluid. The traversal is on the ground(s) that "a search and examination of all the claims would not pose a serious burden on the Examiner". This is not found persuasive. As to the question of burden of search, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Clearly different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is made **FINAL**.

2. Claims 4, 6-9, 28-33, and 44-49 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Applicant timely traversed the restriction (election) requirement in Paper No. 6.

3. This application contains claims drawn to an invention nonelected with traverse in Paper No. 6. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

4. Claims 1-3, 5, 10-27, 34-43 are under examination and will be examined to the extent they read on the species elected in paper # 6 as: inert medium of a macroporous bead, inhibitor of soluble receptors for tumor necrosis factor alpha, and binding partner is an antibody.

Claim Objections

5. Claims 10 and 11 are objected to because of the following informalities:

a. Claims 10 and 11 include species drawn to non-elected inventions. Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-3, 5, 10-27, 34-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-3, 5, 12-27, 34-43 are indefinite for reciting "targeted immune system inhibitor" in claims 1, 12, 20, 22, 26, 27, and 39-42, for the exact meaning of the phrase is not clear. It is not clear what group or groups of molecules are included in the group of "immune system inhibitors".

b. Claims 10 and 11 are indefinite as being structured as an improper Markush claims. (See MPEP 2173.05(h)). Proper Markush claims are in the format of "X is selected from a group consisting of A, B, C, and D," or "the X is A, B, C or D".

NO

c. Claim 11 is indefinite for reciting "homologes" for the exact meaning of the term is not clear. It is unclear what compounds are encompassed by the term "homologes".

d. Claims 12, 14, and those claims dependent therefrom are indefinite for reciting the phrase "naturally-occurring" for the exact phrase is not clear. It is not clear what "binding partners" are encompassed in the phrase.

e. Claim 13 is indefinite for reciting "naturally-occurring binding partner is produced recombinantly" for it is not clear how a naturally occurring binding partner can be produced recombinantly if it is naturally occurring.

f. Claims 15, 18-23, and 25-27 are indefinite for reciting "fragments" for the exact meaning of the term is not clear. It is unclear if the term means antigen binding fragments or fragments that encompass single amino acids.

g. Claim 36 is indefinite for reciting "further comprising after step (a) the steps of" for the exact meaning is not clear. The claim is indefinite because steps (a)-(d) in claim 36 would be between steps (a) and (b) in claim 1, however, this makes no sense.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 14-15, 18-23, and 25-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibodies and antigen binding fragments which specifically bind antigen, does not reasonably provide enablement for fragments of antibodies which would not bind antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

a. Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

b. The claims are broadly drawn to fragments of antibodies which include deletions, substitutions, and antibodies that do not contain a full set of CDRs and as such which would not bind antigen.

c. The specification teaches antibodies specific for sTNFRI (see page 24, lines 26-30). The specification fails to teach fragments of antibodies which would not bind antigen as broadly claimed.

d. The claims are not commensurate in scope with the enablement provided in the specification. The claims encompass fragments of antibodies which include substitutions, deletions, insertions as well as antibodies that do not contain a full set of CDRs and as such would not bind antigen. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that fragments as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions, have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. As evidenced by Adair et al. (WO 91/0996) transfer of CDR regions alone are often not sufficient to provide satisfactory binding activity in the CDR-grafted product (p. 4). Panka et al (Proc Natl Acad Sci USA Vol 85 3080-3084 5/88) demonstrate that a single amino acid substitution of serine for alanine results in decreased affinity. In at least one case it is well known that an amino acid residue in the framework region

is involved in antigen binding (Amit et al Science Vol 233 747-753 1986). Further, a fragment of the heavy chain can be any one of the constant regions (CH1-3) and also may be the hinge region. However, the language also reads on small amino acid sequences which are incomplete regions of the constant region of the antibody. One of skill in the art would neither expect nor predict the appropriate functioning of the antibody as broadly as is claimed. Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1-3, 5, 10-27, 34-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lentz (U.S. Patent 4,708,713, issued 11/24/87, IDS #4) and further in view of Selinsky et al (Immunology 94:88-93, 5/1998, IDS #4) and Maraskovsky et al (U.S. Patent 6,017,527, filed 12/12/96).

a. The claims are summarized as a method of stimulating an immune response in a mammal having a pathological condition comprising obtaining blood from the mammal or human and separating the whole blood into cellular components and a plasma component, contacting the plasma with a recombinant monoclonal or polyclonal antibody or a plurality of such which is covalently attached to a macroporous bead specific for soluble receptors for tumor necrosis factor alpha and the antibody-immune system inhibitor is removed by mechanical or biological or chemical means and combining the cellular component and administering the whole blood to the mammal.

b. Lentz teach a method and system for removing immunosupressive components from the blood of mammals for treating diseases and conditions in deficiencies in the immune response system and the treated blood is returned to the patient to initiate an immune response (see abstract and column 1, lines 1-14). Lentz teach plasmapheresis to separate blood cells from plasma wherein the plasma is treated with immobilized protein A and the plasma is remixed with the blood cells and returned to the patient (see column 1, lines 40-50). Lentz teach the patient can be a mammal or human and the treatment can be performed multiple times with the blood (column 6, line 26). Lentz teach removal of immunosupressive components with a molecular weight of less that 200,000 Daltons (column 2, lines 18-33). Lentz does not teach a recombinant monoclonal antibody specific for soluble receptors for tumor necrosis factor alpha covalently joined to a macroporous bead. These deficiencies are made up for in the teachings of Selinsky et al and Maraskovsky et al.

c. Selinsky et al teach antibodies specific for sTNFRI and Ultraphoresis which is a system that selectively removes plasma components within a defined molecular range which have been implemented as inhibitors of the inflammatory response (see page 88, introduction). Selinsky et al also teach soluble tumor necrosis factor receptor type I is removed by Ultrapheresis (see page 880) and sTNFRI effectively inhibits immune responses in vivo and demonstrates that modulation is a legitimate therapeutic avenue and an anti-human sTNFRI antibody (see page 89 and 92). Selinsky et al also teach "We, therefore, propose the development of methods and/or

reagents capable of specifically removing sTNFRI, or antagonizing its effects in situ, as unconventional, yet promising, strategies for cancer immunotherapy." (See page 92).

d. Maraskovsky et al teach a method of stimulating an immune response in a patient providing a method in which antibodies specific to antigens are immobilized onto a surface such as beads and the blood cells are collected by aphoresis (see column 3, lines 55-56) and the monoclonal antibodies which can be recombinant (column 8, lines 20-21) remove the specific cells and the antibody-antigen complex is removed by a column chromatography method or biological method (see column 4, lines 38-49) and the cells are administered to the patient.

e. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the method of Lentz to stimulate an immune response with antibodies to sTNFRI for removal of sTNFRI which inhibits the immune response as taught by Selinsky et al and immobilize the antibody to a macroporous bead as taught by Maraskovsky et al.

g. One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success in having used the method of Lentz to stimulate an immune response with antibodies to sTNFRI as taught by Selinsky et al and immobilize the antibody to a macroporous bead as taught by Maraskovsky et al because Lentz teach a method of stimulating an immune response with removal of low molecular weight components (called Ultraphoresis) and Selinsky et al teach that sTNFRI is removed from Ultraphoresis and that sTNFRI inhibits the immune response. In addition, one of ordinary skill in the art would have been motivated to and had a

reasonable expectation of success in combining the teachings of Lentz, Selinsky et al and Maraskovsky et al because Selinsky et al teach "We, therefore, propose the development of methods and/or reagents capable of specifically removing sTNFRI, or antagonizing its effects in situ, as unconventional, yet promising, strategies for cancer immunotherapy." (See page 92). Moreover, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success in combining the teachings of Lentz, Selinsky et al and Maraskovsky et al because Maraskovsky et al teach antibodies immobilized on a bead for removal of antigens from a blood sample and administering the altered blood sample to the individual to enhance an immune response. In addition, it would have been obvious to use either a polyclonal antibody or a monoclonal antibody as well as a panel of antibodies that are specific for either one immune system inhibitor or several immune system inhibitors for Lentz teach that there are immunosupressive components in the blood which were separated. In addition, one skilled in the art would know to remove the antibody/antigen complex prior to administering the "altered" biological fluid to the mammal. Thus, it would have been obvious to use the method of Maraskovsky et al to immobilize an antibody of Selinsky which specifically binds to sTNFRI, wherein the sTNFRI inhibits the immune response, and is removed in the method of Lentz using Ultrapheresis.

I. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusions

13. No Claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

15. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Sheela J Huff

SHEELA HUFF
PRIMARY EXAMINER

Respectfully,

Larry R. Helms Ph.D.